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09/595,720	06/16/2000	John C. Cheronis	233/111	1455

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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/595,720	Applicant(s) CHERONIS ET AL.	
	Examiner Lisa V. Cook	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 45* is/are pending in the application.

4a) Of the above claim(s) *29-32 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28,33 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-34 and 45* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicants' response to the office action mailed 11 February 2003 is acknowledged. In amendment-D filed therein a new abstract was submitted. The objection of record in paper #14 is withdrawn. Currently claims 1-28, 33, 45 are pending and under examination.

OBJECTION WITHDRAWN

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the Examiner on form PTO-892 or Applicant on form PTO-1449 has cited the references they have not been considered. (For example, see listing of references).

Applicants have noted that the IDS filed 7/26/00 failed to list one reference cited by the specification at page 2 lines 25-28. A copy will be submitted with a Supplemental IDS as soon as possible. The objection is maintained.

Applicants IDS filed 7/16/03 in paper #16 has been considered. The objection is withdrawn.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Claims 1-28, 33, and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "substantially all" in claim 1 is a relative term which renders the claim indefinite. The term " substantially all " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree (not listed on page 10-11), and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what is intended to be substantially all, will all the molecules bind or not? How will the total binding of all the molecules be assessed (known amounts utilized)? The term should be removed from the claim.

Response to Argument

Applicant contends that the term "substantially all" is perfectly clear when looked at context of the prior art process (i.e. SELEX). However the prior art process is not recited in claim 1. Therefore the rejection is maintained.

In response to applicant's argument that the term " substantially all " is clear to one of ordinary skill in the art from reading the disclosure.

This argument was not found convincing because substantially is a broad term (In re Nehrenberg (CCPA) 126 USPQ 383) and implies clearly that something less than exact correspondence is required (Performed Line Products Co. v Fanner Mfg. Co. (DC Nohio) 124 USPQ 288. Also the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claim remains unclear because what is considered less than all, is not known. The rejection is maintained.

REJECTION MAINTAINED

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

I. Claims 1, 2, 6, 7, 15, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffin et al. (US Patent #5,756,291) in view of Jayasena et al. (US Patent #5,989,823).

Griffin et al. disclose a method of detecting thrombin using a labeled DNA aptamers (nucleic acid aptamer), which specifically bind thrombin (target molecule). The method measures complexes formed when the target molecule is reacted with a mixture of oligonucleotides containing random sequences and sequences that serve as primer for PCR-polymerase chain reaction (the first sample).

A complex is formed with the specific binding sequences but not with the other members of the oligonucleotide mixture. The complex is the separated from uncomplexed oligonucleotides (second sample) and sequenced via successive rounds of selection employing complexation, separation, amplification, and recovery. The target molecules including serum (blood) proteins, kininins, eicosanoids and extracellular proteins. See abstract.

The aptamers may be bound to solid phase/supports and employed to separate target molecules form contaminants (unbound materials) in a sample. See column 12, line 63 through column 13, line 8.

Griffin et al. differ from the instant invention in not specifically reciting that the amount of the target molecule may be directly quantified via aptamer interaction.

However, Jayasena et al. teach methods involving the quantification (measurement of concentration) of a target in a test mixture. The method utilizes a nucleic acid ligand (aptamer) to the target molecule and a ligand beacon. See abstract and figure 2. In one embodiment the methods employ reagents attached to solid supports (immobilized). Diagnostic assays that require quantitative measurements are possible in the method. Column 5 lines 36-40.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to quantitate (determine concentration) of the target molecules as taught by Jayasena et al. in the method utilizing aptamers specific for biomolecules of Griffin et al. because Jayasena et al. taught that diagnostic assays wherein the quantification of target molecules are necessary (i.e. hormone levels or sugar levels) are possible in this simple fluorescence emission detection procedure which could be configured to measure any target molecule. Column 5 lines 10-15 and lines 32-40.

Therefore one having ordinary skill in the art would have been motivated to quantify the target molecule in order to more precisely and accurately determine its presence and characteristics therein, producing results applicable to diagnostic analyses. Column 5 lines 36-40.

Griffin et al. discloses the claimed invention (aptamer utility in target molecule measurements) except for the quantification of the target molecules. Jayasena et al. teach target molecule quantification procedures with aptamers. Column 17 line 65 through Column 18 line 19. It would have been obvious to one having ordinary skill in the art at the time the invention was made to quantify the target molecule since it has been held that the provision of adjustability, where needed, involves only routine skill in the art. In re Stevens, 101 USPQ 284 (CCPA 1954) .

III. Claims 3, 4, 5, 8-14, 18, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffin et al. (US Patent #5,756,291) in view of Jayasena et al. (US Patent #5,989,823) and in further view of Schultz et al. (US Patent #6,180,415).

See Griffin et al. in view of Jayasena et al. are set forth above. Jayasena et al. also teach low abundance molecule detection as defined by the instant specification on page 13 lines 2-5. Specifically low abundance molecules are taught to be present in a sample at nanomolar levels or below. Jayasena et al. teach nanomolar level measurements therein teaching low abundance molecules (See figures 5 and 6 in US Patent# 5,989,823).

Griffin et al. in view of Jayasena et al. differ from the instant invention in not specifically teaching target molecules present in that sample at various dissociations constants (while monitoring the presence of the aptamer) employing support matrixes including beads (particles).

However, Schultz et al. disclose plasmon resonant particle (PRP) method and apparatus for measuring a target molecule in a sample. The method involves the detection of an analyte present in a sample (presence/amount). Abstract.

A ligand is bound to the particles and may be one of a conjugate pair, such as antigen/antibody, hormone/receptor, drug/receptor, effectors/receptor, enzyme/substrate, lipid/lipid binding agent, and complementary nucleic acid strands. Column 5 lines 16-29 and column 8 line 65 through column 9 line 5.

The PRP can be associated with tissue sections, cells, grids, and metals. Column 25 line 64 through column 26 line 26. The methods that employ the inventive new types of probes can bind selected conjugates to the PRP therein detecting low abundance molecules. Column 31, lines 23-33.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to detect low abundance molecules with respect to the concentration of the aptamer in particle configurations (beads) as taught by Schultz et al. in the method of Griffin in view of Jayasena et al. to detect bio-molecules because Schultz et al. taught that the predefined mixtures of PRP [incorporating the ligand] are especially useful in improving the accuracy of detection of low abundance molecules. Column 31, lines 23-33.

III. Claims 16-17, 24-28, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffin et al. (US Patent #5,756,291) in view of Jayasena et al. (US Patent #5,989,823) and in further view of Schultz et al. (US Patent #6,180,415) as applied to claims 3, 4, 5, 8-14, 18, and 24 above, and further in view of Wiegand et al. (WO 96/10576).

See Griffin et al. in view of Jayasena et al. and in further view of Schultz et al. as set forth above.

Griffin et al. in view of Jayasena et al. and in further view of Schultz et al. differ from the instant invention in not disclosing environmental sampling, target molecules including IgE, antibody binding characteristics, and ligands having the apatmer-binding characteristics.

Wiegand et al. disclose these limitations in their method. Oligonucleotide ligands to immunoglobulin IgE are formed and utilized. See page 1. The method is taught to be useful in IgE dependent reactions, which cause allergic disease. The procedure can be used to detect common allergens such as pollen, dust mites, certain food, animal dander, fungal spores, and insect venoms. Page 2, lines 5-6. The method includes nucleic acid ligands that have substantially the same ability to bind IgE as the nucleic ligands (apatmer) used in the assay procedure (Tables 1, 5, and 6 – Page 15, lines 25-31).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect IgE target molecules as taught by Wiegand et al. in the method of Griffin et al. in view of Jayasena et al. and in further view of Schultz et al. because Wiegand taught of IgE's importance in allergic response. Since approximately 20% of the US population is prone to developing an abnormally strong immediate hypersensitivity –allergy, its detection is essential to evaluation and cures. Page 1 line 20 through page 2 line 6. A person of ordinary skill in the art would have had a reasonable expectation of success utilizing and detecting IgE, because Wiegand et al. shown DNA ligands that were operable in this process with high affinity and accuracy. Page 38, lines 3-12.

With respect to the antibody binding characteristics recited in claims 26-28 these limitations are view as inherent properties, which are found in all antibodies. Absent evidence to the contrary they are viewed as obvious limitations found in antibodies.

A claim is anticipated if each element of the claim is found, either expressly described or under principles of inherency, in a single prior art reference, or that the claimed invention was previously known or embodied in a single prior art device or practice.

It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138.

IV. Claims 19, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffin et al. (US Patent #5,756,291) in view of Jayasena et al. (US Patent #5,989,823) and in further view of Sampson et al. (US Patent #6,054,274).

See Griffin et al. in view of Jayasena et al. as set forth above.

Griffin et al. in view of Jayasena et al. differ from the instant invention in not disclosing ligand immobilization on an affinity column or denaturing procedures in their methods.

However, Sampson et al. disclose methods of amplifying target nucleic acid sequence analytes. The method includes repeating signal amplification sequencing (figure 1), denaturing (figure 3), and column separation techniques (polymerization and hybridization). See column 5, line 23 through column 6 line 33.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize denaturing procedures and/or column separation procedures such as hybridization/polymerization as taught by Sampson et al. in the method of Griffin et al. (US Patent #5,756,291) in view of Jayasena et al. (US Patent #5,989,823) because Sampson et al. taught that the inventive method allowed for multiple hybridization and polymerization to produce enhanced detection of a target nucleic acid sequence. Column 3, lines 24-50.

A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such materials, because they were already shown to be operable in the prior art.

One having ordinary skill in the art would have been motivated to do this because of the increased flexibility in detecting and analyzing the target molecule.

Response to Argument

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant contends that the reference of Griffin does not teach the instant invention because they did not specifically recite that the target molecule was quantitated. While the instant claims required the determination of a quantity not qualitative analysis. The argument was carefully considered and not found persuasive. Because the patent to Jayasena et al. (US Patent #5,989,823) teaches aptamer binding of target molecules with the subsequent measure of the target molecule amount/concentration.

Applicant argues that Jayasena et al. teach only quantification utilizing fluorescence however the instant claims do not recite the employment of non-fluorescence quantification. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., non-fluorescence quantification) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore the rejection is maintained.

With regard to the references not teaching "quantitative replicative procedures", it is noted that the disclosure defines this phrase as measurements pf nucleic acids or its expression to determine protein concentration. Page lines 2-3. Since Jayasen et al. teach protein measurements it stands to reason that it reads on Applicants "quantitative replicative procedures". The rejection is maintained.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Applicant contends that the reference of Griffin and Jayasena are not combinable because Griffin is not concerned with quantification, however both references teach the same method SELEX process, therefore it would have been obvious to take the qualitative process (Griffin) to a quantitative process (Jayasena) as presented in the 103(a) rejection above.

Applicant agues that Jayasena et al. teach away from the instant invention because it includes a second nucleic acid ligand in its detection procedure. This argument was carefully considered but not found persuasive because the instant claims utilize open language "comprising", therefore other components may be added to the method to achieve the end point. The rejections are maintained.

5. For reasons aforementioned, no claims are allowed.

Remarks

6. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

Nazarenko et al. (US Paten #5,866,336) disclose methods involving oligonucleotides with molecular energy transfer labels.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4556, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
CM1-7B17
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9/20/03

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